

INTERNATIONAL SEARCH REPORT

Internat.	Application No
PCT/US 95/06540	

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X A	<p>WO-A-94 12219 (SYNERGEN INC ; COX GEORGE N (US); McDERMOTT MARTIN J (US)) 9 June 1994 see page 7 see page 8, line 20 - page 9, line 2 see page 9, line 16 - page 10, line 9; claims 1,2,11,18,19,21,22,24 ---</p> <p>WO-A-90 12874 (GENETICS INST) 1 November 1990 see page 7, line 19 - line 28 see page 13, line 20 - line 33 ---</p> <p>-/-</p>	1-21 1,2,15, 16

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 September 1995

Date of mailing of the international search report

4.0. US. JJ

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentiaan 2
 NL - 2280 HV Rijswijk
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 Fax: (+ 31-70) 340-3016

Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

Internal Application No	PCT/US 95/06540
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO-A-94 22466 (SYNERGEN INC ;COX GEORGE N (US); RUSSELL DEBORAH A (US)) 13 October 1994 see page 8, line 12 - line 22 see page 9, line 1 - line 6 see page 13, line 8 - line 14; claims 1,5-13,17-20,25,28,29,31 ---	1-21
A	J. BIOL. CHEM. (1994), 269(10), 7610-16 CODEN: JBCHA3; ISSN: 0021-9258, 1994 KUAN, CHIEN TSUN ET AL 'Pseudomonas exotoxin A mutants. Replacement of surface exposed residues in domain II with cysteine residues that can be modified with polyethylene glycol in a site-specific manner' see page 7611 ---	1-21
A	BIO/TECHNOLOGY (1990), 8(4), 343-6 CODEN: BTCHDA; ISSN: 0733-222X, 1990 GOODSON, ROBERT J. ET AL 'Site-directed PEGylation of recombinant interleukin-2 at its glycosylation site' cited in the application ---	1,2,8, 10,11,14
P,A	TETRAHEDRON LETT. (1994), 35(35), 6515-16 CODEN: TELEAY; ISSN: 0040-4039, 1994 TANG, WEI ET AL 'Preparation of a new PEGylation reagent for sulfhydryl-containing polypeptide' see the whole document -----	1-21
A	WO-A-92 16221 (SYNERGEN INC) 1 October 1992 see page 19, line 5 - line 19 see page 21, line 6 - line 15 see page 28, line 6 - page 29, line 26 see page 30, line 12 - line 27 see page 33, line 14 - line 37 -----	1-21

INTERNATIONAL SEARCH REPORT

Intern	al Application No
PCT/US 95/06540	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9412219	09-06-94	AU-B-	6048294	22-06-94
		CA-A-	2149048	09-06-94
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WO-A-9012874	01-11-90	US-A-	5166322	24-11-92
		AU-A-	5553790	16-11-90
		EP-A-	0469074	05-02-92
		EP-A-	0668353	23-08-95
		EP-A-	0668354	23-08-95
		JP-T-	4504801	27-08-92
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WO-A-9422466	13-10-94	AU-B-	6626794	24-10-94
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WO-A-9216221	01-10-92	AU-A-	1674292	21-10-92
		EP-A-	0575545	29-12-93
		JP-T-	6506218	14-07-94
		NO-A-	933270	01-11-93
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INTERNATIONAL SEARCH REPORTInt'l. application No.
PCT/US 95/06540**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 21 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int'l. Appl. No.
PCT/US 93/11458

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP,A,0 458 064 (AMERICAN CYANAMID COMPANY) 27 November 1991 see page 2, line 3 - line 7 see page 2, line 50 - page 3, line 6; claims ---	1-25
P,Y	US,A,5 206 344 (NANDINI KATRE) 27 April 1993 see claims; example IC ---	1-25 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
- *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *'A' document member of the same patent family

2

Date of the actual completion of the international search

24 May 1994

Date of mailing of the international search report

14.06.94

Name and mailing address of the ISA
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Fax (+ 31-70) 340-3016

Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

Inten. Appl. Application No
PCT/US 93/11458

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US AN=79:197899 see abstract & BIOPOLYMERS, vol.18, no.2, 1979 pages 383 - 392 GLASS J D ET AL '4-PHOXY-3,5-DINITROBENZOYL POLYETHYLENE GLYCOL REVERSIBLE ATTACHMENT OF CYSTEINE CONTAINING POLYPEPTIDES TO POLYMERS IN AQUEOUS SOLUTIONS.'</p> <p>-----</p>	1-25
2		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/11458

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0458064	27-11-91	AU-B-	639324	22-07-93
		AU-A-	7607591	07-11-91
		JP-A-	6009696	18-01-94
US-A-5206344	27-04-93	AU-A-	5970086	30-01-87
		EP-A,B	0229108	22-07-87
		JP-T-	62503171	17-12-87
		WO-A-	8700056	15-01-87
		US-A-	4917888	17-04-90
		US-A-	4766106	23-08-88

FURTHER INFORMATION CONTINUED FROM PREVIOUS SHEETS

VI. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-57, drawn to pegylated proteins, method of making same and use thereof, Class 514, subclass 12, Class 435 subclasses 69.7 and 240.2, and Class 530, subclasses 410, 395 and 399.

II. Claim 58, drawn to a method of making muteins, Class 435, subclasses 172.1 and 71.2, and Class 530, subclass 402.

The claims of groups I and II are drawn to distinct methods and have a separate status in the art as shown by their different classification. Group I is drawn to the chemical linkage of proteins, whereas Group II is drawn to site-directed mutagenesis for the production of muteins. PCT Rules 13.1 and 13.2 do not provide for multiple distinct methods within a single general inventive concept.

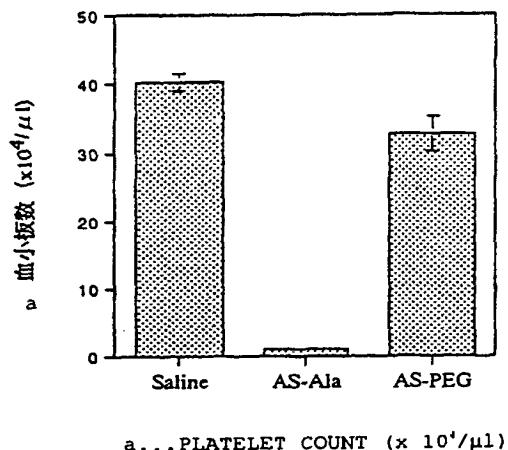
PCT

特許協力条約に基づいて公開された国際出願

(51) 国際特許分類7 C07K 1/14, 14/46, C12N 15/00	A1	(11) 国際公開番号 (43) 国際公開日	WO00/59926 2000年10月12日(12.10.00)
(21) 国際出願番号 PCT/JP00/02127		(22) 国際出願日 2000年3月31日(31.03.00)	
(30) 優先権データ 特願平11/96073 1999年4月2日(02.04.99) 02 Oct 01 / 30 msc JP		(71) 出願人 (米国を除くすべての指定国について) 味の素株式会社(AJINOMOTO CO., INC.)[JP/JP] 〒104-0031 東京都中央区京橋一丁目15番1号 Tokyo, (JP)	(81) 指定国 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, 欧州特許(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許(BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG), ARIPO特許(GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
(72) 発明者 ; および (75) 発明者/出願人 (米国についてのみ) 福地直之(FUKUCHI, Naoyuki)[JP/JP] 影山俊輔(KAGEYAMA, Shunsuke)[JP/JP] 鬼頭守和(KITO, Morikazu)[JP/JP] 猪原孝志(KAYAHARA, Takashi)[JP/JP] 田本浩史(YAMAMOTO, Hiroshi)[JP/JP] 〒210-0801 神奈川県川崎市川崎区鈴木町1-1 味の素株式会社 医薬研究所内 Kanagawa, (JP)		(74) 代理人 豊山 勉, 外(TOYAMA, Tsutomu et al.) 〒103-0004 東京都中央区東日本橋3丁目4番10号 ヨコヤマビル6階 Tokyo, (JP)	添付公開書類 国際調査報告書

(54) Title: PROCESS FOR PRODUCING SUBUNIT PEPTIDE ORIGINATING IN POLYMER PROTEIN

(54) 発明の名称 多量体蛋白質に由来するサブユニットペプチドの製造法



(57) Abstract

A process for producing a subunit peptide originating in a polymer protein which has disulfide bonds in a subunit and between subunits. This process involves the following steps: (a) the step of denaturing the polymer protein or its subunit by using a protein denaturing agent in a solution, and then eliminating the denaturing agent from the solution in the presence of a polyoxyalkyl polyether having a functional group reacting with a thiol group, thereby unwinding the subunit; and (b) the step of separating the subunit, to which the polyoxyalkyl polyether has been bonded, from the solution.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/02122

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC (5): A61K 37/00; C07K 3/00, 13/00, 15/00 US CL : 514/12; 435/69.7, 240.2; 530/410, 395, 399		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	514/12; 435/69.7, 240.2; 530/410, 395, 399	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT¹⁴		
Category ⁶	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	US, A, 4,578,335 (Urdal et al.) 25 March 1986, see entire document	4, 5, 12-14, 17, 18, 26, 28-31, 35, 39
Y	US, A, 4,789,658 (Yoshimoto et al.) 06 December 1988, see entire document	4, 17
Y	Cell, Vol. 61, issued 20 April 1990, Schall et al., "Molecular cloning and expression of a receptor for human tumor necrosis factor", pages 361-370, see entire document.	26, 29
Y	Proceedings of the National Academy of Sciences, Vol. 87, Issued October 1990, Gray et al., "Cloning of human tumor necrosis factor (TNF) receptor cDNA and expression of recombinant soluble TNF-binding protein", pages 7380-7384, see entire document.	26, 28, 29
Y	E. Goldberg et al., "BIOMEDICAL POLYMERS: POLYMERIC MATERIALS AND PHARMACEUTICALS FOR BIOMEDICAL USE", published 1980 by Academic Press (N.Y.), see pages 441-452.	1-57
Y	US, A, 4,847,325 (Shadie et al) 11 July 1989, see entire document.	1-57
<p>* Special categories of cited documents:¹⁶</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"S" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ² 02 June 1992	Date of Mailing of this International Search Report ² 18 JUN 1992	
International Searching Authority ¹ ISA/US	Signature of Authorized Officer ²⁰ Lorraine M. Spector, Ph.D.	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US, A, 4,766,106 (Katre et al) 23 August 1988, see entire document especially abstract, col. 1, c l. 3, lines 57-62, col 4.	1-57
Y	US, A, 4,935,233 (Bell et al.) 19 June 1990, see entire document.	1-57

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

1. Claim numbers , because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. Claim numbers , because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

Please See Attached Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
1-57 (Telephone Practice) (Telephone Practice)

4. As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest:

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.